Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update

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This document is an update to the 2011 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C9 and VKORC1 genotypes and warfarin dosing. Evidence from the published literature is presented for CYP2C9, VKORC1, CYP4F2, and rs12777823 genotype-guided warfarin dosing to achieve a target international normalized ratio of 2–3 when clinical genotype results are available. In addition, this updated guideline incorporates recommendations for adult and pediatric patients that are specific to continental ancestry.

Warfarin is a widely used anticoagulant with a narrow therapeutic index and large interpatient variability in the dose required to achieve target anticoagulation. Common genetic variants in CYP2C9, VKORC1, CYP4F2, and the CYP2C cluster (e.g., rs12777823), plus known nongenetic factors, account for ~50% of warfarin dose variability. This document is an update to the 2011 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2C9 and VKORC1 genotypes and warfarin dosing and aims to assist in the interpretation and use of CYP2C9, VKORC1, CYP4F2, and rs12777823 genotypes to estimate therapeutic warfarin dose among patients with a target international normalized ratio (INR) of 2–3, should clinical genotype results be available to the clinician. The CPIC of the National Institutes of Health’s Pharmacogenomics Research Network develops peer-reviewed gene/drug guidelines that are published and updated periodically on https://cpicpgx.org/guidelines/ and http://www.pharmgkb.org based upon new developments in the field.1 These guidelines were written with a global audience in mind, although the majority of the data that underpin these guidelines arise from people of European ancestry, East Asia, and African Americans.

FOCUSED LITERATURE REVIEW

The Supplement includes a systematic literature review on CYP2C9, VKORC1, CYP4F2 and other relevant genes/genotypes that have been associated with warfarin dosing. This systematic review forms the basis for the recommendations contained in this guideline. Although some of these genes have also been associated with dose of other coumarin anticoagulants, the recommendations below are specific to warfarin.

DRUG: WARFARIN

Warfarin (Coumadin and others) is the most commonly used oral anticoagulant worldwide, with annual prescriptions in the

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The genes with the strongest literature support, and for which we make recommendations for use in warfarin dosing, are CYP2C9, VKORC1, and CYP4F2. Additionally, genomewide association studies have identified an independently significant single nucleotide polymorphism (SNP) in the CYP2C cluster,7 which has also been incorporated into this updated recommendation.

CYP2C9 and warfarin
CYP2C9 is a hepatic drug-metabolizing enzyme in the cytochrome P450 (CYP450) superfamily,8 and is the primary metabolizing enzyme of S-warfarin (Figure 1). CYP2C9 has over 60 known variant alleles (http://www.cypalleles.ki.se/cyp2c9.htm; CYP2C9 allele definition table9). Individuals homozygous for the reference CYP2C9 allele (CYP2C9*1) have the “normal metabolizer” phenotype. Each named CYP2C9 star (*) allele is defined by one or more specific SNPs and, to date, and 18 alleles have been associated with decreased enzyme activity (CYP2C9 allele definition table9). The two most common decreased function alleles among individuals of European ancestry are CYP2C9*2 (c.430C>T; p.Arg144Cys; rs1799853) and CYP2C9*3 (c.1075A>C; p.Ile359Leu; rs1057910)8 CYP2C9 allele frequencies differ between racial/ethnic groups.8,10

In vitro and in vivo studies suggest CYP2C9*2 and *3 impair metabolism of S-warfarin by ~30–40% and ~80–90%, respectively.8 Compared to patients homozygous for CYP2C9*1, individuals who inherit one or two copies of CYP2C9*2 or *3 are at greater risk of bleeding during warfarin therapy,11,12 require lower doses to achieve similar levels of anticoagulation, and require more time to achieve a stable INR11 (Supplemental Table S1). Additional CYP2C9 alleles (CYP2C9*5, *6, *8, and *11) are associated with decreased function of the CYP2C9 enzyme and
contribute to dose variability. These alleles are found with the highest frequency among those of African ancestry, and collectively are more common than \textit{CYP2C9*2} and ‘3 in that population (\textit{CYP2C9 frequency table}).

\textbf{VKORC1} and \textbf{warfarin}

\textit{VKORC1} encodes the vitamin K epoxide reductase protein, the target enzyme of warfarin.\textsuperscript{6} VKORC1 catalyzes the conversion of vitamin K-epoxide to vitamin K, which is the rate-limiting step in vitamin K recycling.\textsuperscript{13}

A common variant upstream of VKORC1 (c.-1639G>A, rs9933231) is significantly associated with warfarin sensitivity and patients with one or two –1639A require progressively lower warfarin doses than –1639G/G homozygotes.\textsuperscript{10,14–18} The –1639G>A polymorphism is present on a haplotype that affects VKORC1 protein expression (\textit{VKORC1 allele definition table}).\textsuperscript{19} Other common VKORC1 SNPs or haplotypes do not further improve warfarin dose prediction.\textsuperscript{10,16} The c.-1639G>A allele frequency varies among different ancestral populations (\textit{VKORC1 frequency table}), and largely explains the differences in average dose requirements between whites, blacks, and Asians.\textsuperscript{10,17} Several rare nonsynonymous \textit{VKORC1} variants confer warfarin resistance (high dose requirements) and are detailed in \textit{Supplemental Table S2}.\textsuperscript{20}

\textbf{CYP4F2} and \textbf{warfarin}

CYP4F2 is a primary liver vitamin K oxidase that catalyzes the metabolism of vitamin K to hydroxy-vitamin K1 and removes vitamin K from the vitamin K cycle\textsuperscript{21} (\textbf{Figure 1}). It acts as an important counterpart to VKORC1 in limiting excessive accumulation of vitamin K. The nonsynonymous variant \textit{CYP4F2*3} (c.1297G>A; p.Val433Met; rs2108622) was first shown to affect enzyme activity and associated with warfarin dose in three independent white cohorts (\textit{CYP4F2 allele definition table}).\textsuperscript{21–24} Furthermore, including this \textit{CYP4F2} variant in warfarin dosing models that included \textit{CYP2C9}, VKORC1, and clinical factors improved the accuracy of dose prediction.\textsuperscript{25} This correlation has been confirmed in subsequent studies with those of European and Asian ancestry, although not those of African ancestry.\textsuperscript{26,27} Two large meta-analyses (one in Han Chinese that pulled in substantial Chinese literature) provide the best estimates for the influence data of \textit{CYP4F2*3} on warfarin dose requirements.\textsuperscript{26,27} They suggest statistically significant but modest impacts of 8–11% higher warfarin doses in A allele carriers (\textit{Supplemental Table S3}).

\textbf{CYP2C rs12777823} and \textbf{warfarin}

rs12777823 is a SNP in the \textit{CYP2C} cluster near the \textit{CYP2C18} gene on chromosome 10 and is associated with a clinically relevant effect on warfarin dose through significant alterations in warfarin clearance, independent of \textit{CYP2C9*2} and ‘3.\textsuperscript{7} This association was first identified through a genome-wide association study in African Americans (\textit{P} = 1.51×10\textsuperscript{-6}) and confirmed in a replication cohort (\textit{P} = 5.04×10\textsuperscript{-5}); meta-analysis of the two cohorts together produced a \textit{P} value of 4.5×10\textsuperscript{-12}. This study concluded that African Americans who are heterozygous or homozygous for the rs12777823 A allele require a dose reduction of ~7 or 9 mg/week, respectively.\textsuperscript{7} Regression analysis showed that addition of this SNP improves the dosing algorithm published by the International Warfarin Pharmacogenetics Consortium (IWPC) by 21%. Further studies have demonstrated the importance of this SNP in African Americans.\textsuperscript{28} Although this variant is common in other ethnic populations, an association with warfarin dose has only been detected among African Americans, suggesting it is not the underlying cause but likely inherited with other variant(s) on a haplotype that influences warfarin dose in this population. Of note, an association was not observed in a cohort of Egyptians, thus it is not possible to make broad statements about this allele in people of continental African ancestry. Most African Americans are of West African ancestry; it is unknown whether similar associations are present in individuals from other parts of Africa.

\textbf{Genetic test interpretation}

\textbf{CYP2C9.} Clinical laboratories typically report \textit{CYP2C9} genotype results using the star (*) allele nomenclature system and an interpretation that includes a predicted metabolizer phenotype (\textit{CYP2C9 allele definition table}). Most FDA-approved \textit{CYP2C9} tests include only ‘2 and ‘3, which is not as informative for African ancestry populations; however, some clinical laboratories may offer expanded \textit{CYP2C9} panels validated as laboratory developed tests (LDTs) (for allele frequencies see: \textit{CYP2C9 frequency table}).

\textbf{VKORC1.} Clinical laboratories typically report \textit{VKORC1} genotype results by c.-1639G>A (or the linked 1173C>T; rs9934438) genotype (e.g., G/A) and an interpretation on warfarin sensitivity (\textit{VKORC1 allele definition table}). Most commercial genotyping platforms do not detect rare \textit{VKORC1} variants that have been associated with warfarin resistance (\textit{VKORC1 frequency table}).

\textbf{CYP4F2.} Although not as commonly tested for as \textit{CYP2C9} and \textit{VKORC1}, some clinical laboratories may also test for \textit{CYP4F2} using a targeted genotyping laboratory developed test to detect \textit{CYP4F2*3} (c.1297G>A; p.Val433Met; rs2108622) variant (\textit{CYP4F2 allele definition table}). Results are typically reported by nucleotide (e.g., G/A), amino acid (e.g., Val/Met) or star (*) allele (‘1/‘3) genotype and an interpretation related to warfarin dosing.

\textbf{CYP2C rs12777823.} Given the recent identification of the association between rs12777823 (g.9640550G>A) and warfarin dosing among African Americans, most clinical laboratories do not currently include this non-coding variant in their warfarin pharmacogenetic genotyping panels. However, the increasing accessibility of clinical research genomics programs that return actionable results and the notable effect of this variant among African Americans suggests that some patients may have genotype results for this variant in the future. Results would likely be reported by genotype (e.g., G/A) and an interpretation related to warfarin dosing.
Genetic test options
Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at the Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr/).

Incidental findings
No diseases have been linked to common CYP2C9 variants independent of drug metabolism and response. Similarly, no diseases have been consistently linked to common VKORC1 and CYP4F2 variants that are interrogated in warfarin response tests. However, homozygosity for rare coding mutations in VKORC1 are a known cause of combined deficiency of vitamin K-dependent clotting factors-2 (VCKFD2), which is a rare and potentially fatal bleeding disorder that can be reversed by oral administration of vitamin K.

Linking genetic variability to variability in drug-related phenotypes
Common variants in CYP2C9, VKORC1, and CYP4F2 account for up to 18%, 30%, and 11% respectively, of the variance in stable warfarin dose among patients of European ancestry,10,16,17,30,31 but because of differing allele frequencies across populations, these variants explain less of the dose variability in patients of other ancestries. In particular, CYP2C9*2 is virtually absent in Asians, and additional CYP2C9 alleles (e.g., *5, *6, *8, and *11 alleles) occur almost exclusively in persons of African ancestry and contribute to dose variability in this population. Other genes of potential importance are discussed in the Supplemental Material.

Published in 2013, the European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) and Clarification of Optimal Anticoagulation through Genetics (COAG) trials examined the efficacy of genotype-guided warfarin dosing in randomized controlled trials.32,33 In a homogenous European population, the EU-PACT trial showed shorter time to stable dose, improved percent time in therapeutic range, and reduced number of episodes with an INR >4 using a pharmacogenetic dosing algorithm compared to standard dosing.33 The COAG trial was conducted in an ethnically diverse cohort with 27% of participants of African ancestry. Overall, COAG did not show a difference in time to stable dose, percent time in therapeutic range, reduction in number of episodes with INR >4 or <2, or bleeding risk with a pharmacogenetic dosing algorithm compared to a clinical algorithm. In nonblacks, the pharmacogenetic dosing algorithm arm had more patients whose stable dose was within 1 mg per day of the algorithm-predicted dose (57 vs. 39%, respectively). In contrast, the pharmacogenetic dosing algorithm was less accurate at predicting within 1 mg/day of the stable dose than the clinical algorithm in blacks (38 vs. 48%, respectively).32 Blacks were more likely to have an INR above 4 with pharmacogenetic dosing, which could be due to the genotyping panel in the COAG trial being limited to CYP2C9*2, *3, and VKORC1 c.-1639G>A. Other variants that influence warfarin dose and are more common in blacks (i.e., CYP2C9*5, *6, *8, and *11 and rs12777823) were not genotyped in the COAG trial and their absence likely led to significant overdosing in patients with these alleles.10,34 Consequently, this updated CPIC guideline recommends against pharmacogenetic dosing of warfarin in blacks when only CYP2C9*2 and *3 genotype results are available.

The Genetics-Informatics Trial (GIFT) was a randomized controlled trial examining the effectiveness and safety of genotype-guided dosing versus clinical algorithm dosing in orthopedic patients with a composite outcome that included symptomatic and asymptomatic venous thromboembolism, major hemorrhage, INR ≥ 4, and death.35 It is the first warfarin pharmacogenetics trial powered for clinical outcomes. GIFT included genotyping for CYP2C9*2 and *3, CYP4F2*3, and VKORC1-1639, but did not include the African-specific CYP2C9 alleles or rs12777823. The results of GIFT were presented in early 2017 and revealed a 27% reduction in the composite outcome with genotype-guided versus clinical algorithm dosing, documenting the clinical benefits of a genotype guided approach to warfarin dosing. (https://www.sciencedaily.com/releases/2017/03/170320091104.htm)

Therapeutic Recommendations: Adults
Recommendations for warfarin maintenance (chronic) dosage based on genetic information. We use the three-tiered rating system described previously (and in the Supplemental Material)1 in which ratings of strong, moderate, and optional are applied based on the evidence reviewed. The recommendations for dosing based on genotype contained herein include recommendations and are derived from numerous observational and prospective studies, and randomized trials that suggest the ability to more accurately identify stable therapeutic warfarin dose requirements through the use of both genetic and clinical information. Data from prospective studies and randomized controlled trials are equivocal on whether the improvement in dosing prediction by pharmacogenetics dosing leads to improved clinical outcomes. The majority of the literature underpinning these guidelines arises from individuals of European ancestry, African Americans, and East Asians. However, the more limited literature in other populations generally suggests the guidelines are appropriate in them also.

Numerous studies have derived warfarin dosing algorithms that use both genetic and nongenetic factors to predict warfarin dose.16,17,36,37 Two algorithms perform well in estimating stable warfarin dose16,17 and were created using more than 5,000 subjects, although as noted above, more recent data suggest they do not perform acceptably in African Americans when used without modification for CYP2C9 alleles frequently found in the African population.32 The Gage and IWPC algorithms or minor adjustments to them have also been the algorithms used in both randomized controlled trials and most of the prospective dosing studies. Dosing algorithms using genetic information outperform nongenetic clinical algorithms and fixed-dose approaches in dose prediction, except in African Americans when the algorithm only includes CYP2C9*2 and *3.16,17,35,37 Genetics-based algorithms also better predict warfarin dose than the FDA-approved warfarin label table.8 Pharmacogenetic algorithm-based warfarin dosing. This guideline recommends that pharmacogenetic warfarin dosing be accomplished through the use of one of the pharmacogenetic dosing

Pharmacogenetic algorithm-based warfarin dosing.
algorithms described above, as summarized in Figure 2. These algorithms, as originally published, are available in the Supplement and the dosing algorithm published by IWPC is also online at http://www.pharmgkb.org/do/serve?objId=PA162372936&objCls=Dataset#tabview. The two algorithms provide very similar dose recommendations. The clinical and genetic information used in one or both algorithms is shown in Text Box 1.

Figure 2 Dosing recommendations for warfarin dosing based on genotype for adult patients. (a) “Dose clinically” means to dose without genetic information, which may include use of a clinical dosing algorithm or standard dose approach. (b) Data strongest for European and East Asian ancestry populations and consistent in other populations. (c) 45–50% of individuals with self-reported African ancestry carry CYP2C9*5, *6, *8, and *11 were not tested, dose warfarin clinically. Note: these data derive primarily from African Americans, who are largely from West Africa. It is unknown if the same associations are present for those from other parts of Africa. (d) Most algorithms are developed for the target INR 2-3. (e) Consider an alternative agent in individuals with genotypes associated with CYP2C9 poor metabolism (e.g., CYP2C9*3/*3, *2/*3, *3/*3) or both increased sensitivity (VKORC1 A/A or A/A) and CYP2C9 poor metabolism. (f) See the EU-PACT trial for pharmacogenetics-based warfarin initiation (loading) dose algorithm with the caveat that the loading dose algorithm has not been specifically tested or validated in populations of African ancestry. (g) Larger dose reduction might be needed in variant homozygotes (i.e., 20–40%). (h) African American refers to individuals mainly originating from West Africa.

Text Box 1. Patient characteristics utilized in the Gage (16), or IWPC (17) algorithms or both

- **Age**
- **Sex**
- **Race**
- **Weight**
- **Height**
- **Smoking status**
- **Warfarin indication**
- **Target INR**
- **Interacting drugs**
  - Inhibitors: Amiodarone, statins, sulfamethoxazole, azole antifungals
  - Inducers: Rifampin, phenytoin, carbamazepine
- **Genetic variables**
  - CYP2C9 genotype
  - VKORC1 genotype
  - Gage algorithm can also incorporate CYP4F2 and GGCGX genotypes
algorithm is or is not incorporating genotypes beyond \( CYP2C9 ^{\ast 2} \) and \( CYP2C9 ^{\ast 3} \) and \( VKORC1 \), which are the only three genotypes in the original version of both algorithms.

Pharmacogenetics-informed loading (or initiation) dose calculations. The use of a different initial warfarin dose (or “loading dose”) is somewhat controversial and plays different roles in different regions of the world, based on experience and local standards. Recent data from a diverse US-based cohort suggest that failure to provide a loading dose in patients with zero or one variant alleles in \( VKORC1 \) or \( CYP2C9 \) may delay time to therapeutic INR and reduce time in therapeutic range in the initial month of therapy. Algebraically guided loading dose approach was developed by Avery et al \(^{57} \) and a slightly modified version was successfully implemented in the EU-PACT trial.\(^ {33} \) In COAG \( CYP2C9 \) variant alleles were not considered for the initial dose, providing a small loading dose on day 1. Whether differences in loading dose strategies between the EU-PACT and COAG trials contributed to differing results is not known. If loading doses are to be used, a genetically informed approach to calculating the loading dose may be helpful. The majority of the experience with a genetically informed loading regimen is in those of European ancestry. Determination of maintenance dose would be as described above.

Non-African ancestry recommendation. In patients who self-identify as non-African ancestry, the recommendation, as summarized in Figure 2, is to: 1) calculate warfarin dosing using a published pharmacogenetic algorithm, \(^ {16,17} \) including genotype information for \( VKORC1-1639G>A \) and \( CYP2C9^{\ast 2} \) and \( ^{*3} \). In individuals with genotypes associated with \( CYP2C9 \) poor metabolism (e.g., \( CYP2C9 ^{\ast 2}/^{\ast 3} \), \( ^{*3}/^{*3} \)) or both increased sensitivity (\( VKORC1-1639 \) A/A) and \( CYP2C9 \) poor metabolism, an alternative oral anticoagulant might be considered. \(^ {12} \) The bulk of the literature informing these recommendations is in European and Asian ancestry populations, but consistent data exist for other non-African populations. These recommendations are graded as STRONG. 2) If a loading dose is to be utilized, the EU-PACT loading dose algorithm that incorporates genetic information could be used.\(^ {33} \) This recommendation is OPTIONAL. 3) While \( CYP2C9^{\ast 5} \), \( ^{*6} \), \( ^{*8} \), or \( ^{*11} \) variant allele(s) are commonly referred to as African-specific alleles, they can occur among individuals who do not identify as, or know of, their, African ancestry. If these variant alleles are detected, decrease calculated dose by 15–30% per variant allele or consider an alternative agent. Larger dose reductions might be needed in patients homozygous for variant alleles (i.e., 20–40%, e.g., \( CYP2C9^{\ast 2}/^{\ast 5} \)). This recommendation is graded as OPTIONAL. 4) If the \( CYP4F2^{\ast 3} \) (i.e., c.1297A, p.G333Met) allele is also detected, increase the dose by 5–10%. This recommendation is also considered OPTIONAL. 5) The data do not suggest an association between \( rs12777823 \) genotype and warfarin dose in non-African Americans, thus \( rs12777823 \) should not be considered in these individuals (even if available).

African ancestry recommendation. In patients of African ancestry, \( CYP2C9^{\ast 5} \), \( ^{*6} \), \( ^{*8} \), \( ^{*11} \) are important for warfarin dosing. If these genotypes are not available, warfarin should be dosed clinically without consideration for genotype. If \( CYP2C9^{\ast 5} \), \( ^{*6} \), \( ^{*8} \), and \( ^{*11} \) are known, then the recommendation, as shown in Figure 2, is to: 1) calculate warfarin dose using a validated pharmacogenetic algorithm, including genotype information for \( VKORC1-1639G>A \) and \( CYP2C9^{\ast 2} \) and \( ^{*11} \). 2) If the individual carries a \( CYP2C9^{\ast 5} \), \( ^{*6} \), \( ^{*8} \), or \( ^{*11} \) variant allele(s), decrease calculated dose by 15–30%. Larger dose reductions might be needed in patients who carry two variant alleles (e.g., \( CYP2C9^{\ast 5}^{*6} \)) (i.e., 20–40% dose reduction). 3) In addition, \( rs12777823 \) associated with warfarin dosing in African Americans (mainly originating from West Africa). Thus, in African Americans a dose reductions of 10–25% in those with \( rs12777823 \). A/G or A/A genotype is recommended. These recommendations are considered MODERATE.

In individuals with genotypes that predict \( CYP2C9 \) poor metabolism or who have increased \( VKORC1-1639 \) A/A and \( CYP2C9 \) poor metabolism, an alternative oral anticoagulant should be considered (see Supplemental Material for definitions of strength of recommendations). As noted above, for non-African ancestry, if a loading dose is to be used, the EU-PACT algorithm\(^ {33} \) that incorporates genetic information could be used to calculate loading dose. This recommendation is OPTIONAL. The data do not support an impact on clinical phenotype for \( CYP4F2 \) on warfarin dosing in those of African ancestry and so no recommendation is made for use of \( CYP4F2 \) genotype data in blacks.

Recommendations for pediatric patients. As detailed in Supplemental Table S7, there is strong evidence for the use of \( CYP2C9^{\ast 2} \) and \( ^{*3} \) and \( VKORC1-1639G>A \) genotype to guide warfarin dosing in children of European ancestry. The studies in Japanese pediatric individuals are conflicting, as \( VKORC1 \) and \( CYP2C9 \) could not be adequately evaluated due to the low numbers of \( CYP2C9 \) variant carriers. For other
Other considerations

Given the effects of CYP2C9 on warfarin clearance, and given that the CYP2C9 variant alleles are associated with reduced warfarin clearance, CYP2C9 genotype may influence time to onset and offset of anticoagulation, as measured by INR. The Supp-
lemental Material summarizes other considerations in the dos-
ing of warfarin, including clinical factors and interacting drugs, some of which are included in the pharmacogenetic dosing algo-
rithms (see Text Box 1). Other genes of potential importance are
detailed in the Supplemental Material and Supplemental Table S6, including CALU and GGCX. Most clinical genotyping
platforms do not include these genes, nor do the dosing tables or
published algorithms. The Supplemental Material also discusses
incorporation of genetic information into the initial dose, and
alternatives to warfarin.

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

Incorporation of genetic information has the potential to shorten
the time to stable INR, increase the time within the therapeutic
INR range, and reduce underdosing or overdosing during the ini-
tial treatment period. If these benefits are achieved, they could
result in a reduced risk of bleeding and thromboembolic
events. There are also potential risks. For example, using
genetic information to guide dosing may lead to false security and
inadequate INR monitoring. In particular, there are risks of
using pharmacogenetic dosing in those of African ancestry if only
CYP2C9 *2 and *3 alleles are included. Genetic-guided dosing
may increase the risk for overdosing or underdosing, especially in
individuals who carry rare or untested variants and are assigned
as “wild-type” by default. The cost–benefit of genetic-guided
therapy depends on the cost of genotyping and the reduction in
adverse events, and most insurance plans do not currently pay
for warfarin pharmacogenetic testing. Although there is substan-
tial evidence associating CYP2C9 and VKORC1 variants with
warfarin dosing, randomized clinical trials have demonstrated
inconsistent results in terms of clinical outcomes (see Linking
genetic variability to variability in drug-related phenotypes,
above). Although genotyping is reliable when performed in quali-
fied laboratories, an additional risk is an error in genotyping or
reporting of genotype. Genotypes are life-long test results, so such
error could have long-term adverse health implications.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL
MISUSE OF GENETIC TESTS

Many pharmacogenetic dosing algorithms are developed for a tar-
get INR of 2–3 and so their utility for estimating therapeutic
warfarin doses with other target INR ranges is uncertain; howev-
er, some algorithms accommodate the target INR explicitly. Phar-
macogenetic-guided warfarin dosing does not alter the
requirements for regular INR monitoring. There are patients for
whom genetic testing is likely to be of little or no benefit, includ-
ing those who already have had long-term treatment with stable
warfarin doses and those who are unable to achieve stable dosing
due to variable adherence. The greatest potential benefit is early
in the course of therapy (before therapy initiation or in the early
days of therapy). It is likely that patients on therapy for many
weeks to months, with careful INR monitoring, will derive little
benefit from subsequent warfarin pharmacogenetics testing.

DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC)
guidelines reflect expert consensus based on clinical evidence and
peer-reviewed literature available at the time they are written and
are intended only to assist clinicians in decision-making and to
identify questions for further research. New evidence may have
emerged since the time a guideline was submitted for publication.
Guidelines are limited in scope and are not applicable to inter-
ventions or diseases not specifically identified. Guidelines do not
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SUPPLEMENTARY MATERIAL is linked to the online version of the arti-
cle at www.cpt-journal.com

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CONFLICTS OF INTEREST

J.A.J. is on the CPIC Steering Committee and has no conflicts of
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cientific advisors to the Rxight Pharmacogenetic Program. S.A.S. is
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